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Complementary Therapies and Integrative Oncology in Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **This chapter aims to differentiate between "alternative" therapies, often promoted falsely as viable options to mainstream lung cancer treatment, and complementary therapies, adjunctive, effective techniques that treat symptoms associated with cancer and its mainstream treatment, and to describe the evidence base for use of complementary therapies.**
Methods and design: **A multidisciplinary panel of experts in oncology and integrative medicine evaluated the evidence for complementary (not alternative) therapies in the care of patients with lung cancer. Because few complementary modalities are geared to patients with only a single cancer diagnosis, symptom-control research conducted with other groups of patients with cancer was also included. Data on complementary therapies such as acupuncture, massage therapy, mind-body therapies, herbs and other botanicals, and exercise were evaluated. Recommendations were based on the strength of evidence and the risk-to-benefit ratio.**
Results: **Patients with lung and other poor-outlook cancers are particularly vulnerable to heavily promoted claims for unproved or disproved "alternatives." Inquiring about patients' use of these therapies should be routine because these practices may be harmful and can delay or impair treatment. Mind-body modalities and massage therapy can reduce anxiety, mood disturbance, and chronic pain. Acupuncture assists the control of pain and other side effects and helps reduce levels of pain medication required. Trials of acupuncture for chemotherapy-induced neuropathy and posttho-racotomy pain show promising results. Herbal products and other dietary supplements should be evaluated for side effects and potential interactions with chemotherapy and other medications.**
Conclusions: **Complementary therapies have an increasingly important role in the control of symptoms associated with cancer and cancer treatment.** ***(CHEST 2007; 132:340S–354S)***

Key words: acupuncture; botanicals; cancer; complementary and alternative medicine; complementary therapies; fitness; herbs; integrative medicine; massage therapy; mind-body therapies; music therapy; oncology

Abbreviations: CAM = complementary and alternative medicine; MSKCC = Memorial Sloan-Kettering Cancer Center; NIH = National Institutes of Health

A distinction between "complementary" and "alternative" therapies is required. Complementary therapies, used as adjuncts to mainstream care, are supportive measures that help control symptoms, enhance well-being, and contribute to overall patient care.[1] Alternative therapies, conversely, are often

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Table 1—*Categories and Examples of Complementary and Alternative Therapies*

Biologically Based Practices	Herbal remedies, vitamins, other dietary supplements
Mind-body techniques	Meditation, guided imagery
Manipulative and body-based practices	Massage, reflexology
Energy therapies	Magnetic field therapy
Ancient medical systems	Traditional Chinese medicine, ayurvedic medicine, acupuncture

unproved or disproved, promoted for use instead of mainstream treatment, or are offered as viable therapeutic options. This is especially problematic in oncology, when delayed treatment can diminish the possibility of remission and cure.[2] Over time, some complementary therapies are proven safe and effective. These become integrated into mainstream care, producing integrative oncology, a combination of the best of mainstream cancer care and rational, data-based, adjunctive complementary therapies.[3]

Most complementary and alternative medicine (CAM) practices can be loosely grouped into five categories according to the National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (Table 1). The therapies in these categories are quite mixed; some are helpful, others are bogus. There is also considerable overlap among the categories. For example, traditional Chinese medicine uses biologically active botanicals and acupuncture. Yoga has mind-body and manipulative components and Ayurvedic principles in theory. Some interventions, such as music therapy, do not fit easily into a category (Table 1).

Most complementary therapies are not specific to a particular cancer diagnosis. Instead, they are used typically to treat symptoms shared by patients across most cancer diagnoses. This is generally appropriate because symptoms tend to stem less from the primary diagnosis than from involvement of a particular organ or toxicities associated with treatment, which evoke similar symptoms in patients across cancer diagnoses. For example, bone metastases cause pain regardless of whether the primary lesion was from breast or prostate; chemotherapy-induced nausea and vomiting are associated more closely with the emetogenic potency of the drug used than with the underlying cancer diagnosis. In these guidelines, we summarize data relevant to clinical problems encountered by patients with lung cancer and make practical recommendations based on the strength of the evidence.

The use of complementary therapies is common among cancer patients. "Alternative therapies" draw a far smaller percentage of patients but remain a serious problem. The difference between "complementary" and "alternative" therapies is important and essential to recognize. "Alternative" therapies are typically promoted as literal, viable options for use *in lieu* of mainstream care. They are not. There are no viable "alternatives" to mainstream care. Instead, these are bogus products and regimens that draw patients with unsubstantiated, often fanciful, claims of easy cure. Typically they are unproven or disproved, invasive, and biologically active. Such "alternatives" are heavily promoted to all patients with all cancer diagnoses, and patients with lung and other poor-outlook cancers are particularly vulnerable.

The Society for Integrative Oncology and its MEDLINE-listed journal, formed by leading oncologists and major cancer centers and organizations, deliberately uses terminology meant to distinguish itself from purveyors of foolish therapies and bogus "alternatives," as well as to display quality research and appropriate application of useful, adjunctive complementary modalities (www.IntegrativeOnc.org). This chapter includes minimal discussion of useless approaches and recommends that readers obtain additional information about them at www.mskcc.org/aboutherbs or www.quackwatch.org.

Although the external validity of most clinical trials in adult oncology may be questioned because only a small fraction of eligible patients participate, this is a lesser problem in trials involving complementary therapies because they address symptom control and quality of life with noninvasive therapies that produce few if any side effects. Patients generally are more amenable to such studies.

This chapter addresses complementary therapies, which are noninvasive adjuncts to mainstream care. Complementary therapies are applied not to treat lung cancer or any other malignancy but rather to treat the symptoms associated with cancer and its mainstream treatments. This category also includes the study of herbs and other botanicals. Clinical trials of some herbs and other botanicals aside, few complementary modalities are geared to patients with only a single cancer diagnosis. Thus, symptom-control research conducted with other groups of cancer patients is noted as well because these data are likely to have broad applicability in lung cancer practice.

Health-care professionals should be able to provide evidence-based, patient-centered advice to guide patients to receive benefit while avoiding harm. A panel of experts in oncology and integrative medicine was assembled to evaluate the current level of evidence regarding complementary (not alternative) therapies relevant to the care of patients with lung cancer. Specific recommendations are made based on the strength of evidence and the risks/benefit ratio.

Because the use of CAMs by cancer patients is common, a strong recommendation is made to inquire about the use of these therapies as a routine part of the initial evaluation of lung cancer patients. Complementary therapies can be helpful in symptom control, whereas the use of alternative therapies can delay or impair treatment. It is strongly recommended that guidance should be provided in an open, evidence-based, and patient-centered manner by a qualified professional to those patients who use or who are interested in CAM so that they can approach these therapies appropriately.

Mind-body modalities are strongly recommended to be incorporated into a multidisciplinary approach in reducing anxiety, mood disturbance, or chronic pain in cancer patients. A strong recommendation is made to consider massage therapy as part of a multimodality treatment approach in lung cancer patients who experience anxiety or pain. Application of deep or intense pressure during massage therapy should be avoided near cancer lesions or anatomic distortions such as postoperative changes as well as in patients with a bleeding tendency (weak recommendation). Therapies based purely on the putative manipulation of bioenergy fields or other nonrational ideas are considered bogus and are not recommended.

Acupuncture is strongly recommended as a complementary therapy for pain control when pain is poorly controlled, when side effects from other modalities are clinically significant, or when reducing the amount of pain medicine becomes a clinical goal. Acupuncture is also strongly recommended as a complementary therapy when nausea and vomiting associated with chemotherapy are poorly controlled or when side effects from other modalities are clinically significant. Electrostimulation wristbands should not be used to reduce chemotherapy-induced nausea and vomiting because it appears to become a conditioned stimulus. The value of acupuncture in treating nicotine addition, dyspnea, or fatigue is not supported by conclusive evidence. A trial[4] of acupuncture for chemotherapy induced neuropathy showed positive results. Acupuncture for postthoracotomy pain is undergoing study. Given some reports of potential benefit, a trial of acupuncture is acceptable when symptoms are severe and not responding adequately to other treatments. Acupuncture is generally safe when performed by qualified practitioners. Caution should be exercised in patients with bleeding tendency.

Taking dietary supplements can be beneficial in some circumstances and harmful in others. Supplementation of vitamin B12 and folic acid is required in patients receiving pemetrexed treatment. A strong recommendation is made for dietary supplements used by patients, particularly herbal products, to be evaluated for side effects and potential interaction with other drugs. Those that are likely to interact with chemotherapeutic agents should not be used during chemotherapy.

It is strongly recommended that patients be advised to avoid the use of "alternative" therapies *in lieu* of mainstream care. Such practice can lead to significant harm to lung cancer patients because it delays effective treatment and causes unpredictable adverse effects.

Despite the long history of many complementary therapies, only a few have been evaluated with modern scientific research tools in a handful of indications. A large gap exists between our current level of scientific evidence and what we need to provide evidence-based advice. More rigorous scientific research is being conducted to enrich our knowledge base. Meanwhile, the risk-to-benefit ratio associated with the strong recommendations noted is consistent with good clinical care. In the context of a devastating diagnosis that most patients do not survive, nontoxic complementary therapies can successfully provide symptom relief to lung cancer patients.

Detailed Methodology

A multidisciplinary panel of experts in oncology was gathered to prepare this chapter. The team included the following: thoracic medical oncologist Jorge E. Gomez, MD, at Memorial Sloan-Kettering Cancer Center (MSKCC); radiation oncologist and acupuncturist Peter A. S. Johnstone, MD, at Emory University School of Medicine; Gary E. Deng, MD, PhD, an internist specializing in integrative oncology at MSKCC; Nagi Kumar, PhD, a nutritionist/researcher at the Moffitt Cancer Center; Andrew Vickers, PhD, a biostatistician/research methodologist specializing in integrative oncology; and corresponding author Barrie Cassileth, Chief of Integrative Medicine Service, MSKCC.

Sources searched included English-language clinical trials or reviews in MEDLINE and relevant chapters in recent major oncology text books and government Web sites. MEDLINE was searched for articles published from 1980 to 2006. These searches were conducted from December 2005 through April 2006.

Limitations: Gaps in Research

Despite the long history of most complementary modalities, rigorous scientific research on these therapies is a recent phenomenon. The research is

further limited by lack of sufficient funding, lack of qualified investigators, and methodologic and ethical issues unique to studying complementary therapies. Therefore, gaps in research are the norm rather than the exception in this field, and these gaps represent the major limitation. Many complementary therapies derived from complete traditional medical system were used historically to treat almost every ailment. Only a few modalities have been evaluated with modern scientific research tools in a few indications. Those data related to lung cancer are discussed in this article. Our current knowledge base is simply insufficient. A tremendous amount of work needs to be performed before we can offer more comprehensive evidence-based recommendations.

Integrative medicine evaluated the evidence for complementary (not alternative) therapies in the care of lung cancer patients. Because few complementary modalities are geared to patients with only a single cancer diagnosis, symptom-control research conducted with other groups of cancer patients was also included. Data on complementary therapies such as acupuncture, massage therapy, mind-body therapies, herbs and other botanicals, and exercise were evaluated. Recommendations were based on the strength of evidence and the risk-to-benefit ratio.

Recommendations and Discussion

The recommendations are organized according to modalities. Within each modality, recommendations supported by a strong level of evidence are made and discussed first (grade A and B). Recommendations are presented in text boxes for easy recognition. Selected topics where only grade C recommendations can be made are then discussed. These topics are selected based on their clinical significance. Such selectiveness is necessary because of the nascent nature of research in this area. For many issues relevant to lung cancer patients, there is currently insufficient evidence to make any meaningful recommendation. For other issues, relevant but not exclusive to lung cancer, existing data from other cancer diagnoses can be safely extrapolated.

Use of CAM

Recommendation

1. It is recommended that all patients with lung cancer be asked specifically about the use of CAM. Grade of recommendation, 1C

Rationale and Evidence: The most comprehensive and reliable findings on Americans' use of CAM in general come from the National Center for Health Statistics 2002 National Health Interview Survey. The National Center for Health Statistics is an agency of the Centers for Disease Control and Prevention.[5] Of 31,044 adults surveyed, 75% used some form of CAM. When prayer specifically for health reasons is excluded, the percentage is 50%.

By various accounts, 10% to > 60% of cancer patients have used CAM, depending primarily on the definitions applied.[6–10] The Datamonitor 2002 Survey indicated that 80% of cancer patients used an alternative or complementary modality.[11] There is some indication of a growth in CAM use by cancer patients in recent years.[12] When compared to other cancer diagnoses, prevalence of CAM use was the highest in lung cancer patients (53%) according to a nationwide survey in Japan.[13] This is not the case in a Europe-wide survey, in which 24% of lung cancer patients reported CAM use.[14] Consistent across all surveys, CAM users typically are younger, more educated, and more affluent, representing a more health-conscious segment of the population who are willing and able to play an active role in their own care.

Recommendation

2. It is recommended that all patients with lung cancer be given guidance about the advantages and disadvantages of complementary therapies in an open, evidence-based, and patient-centered manner by a qualified professional. Grade of recommendation, 1C

Rationale and Evidence: Surveys show that most cancer patients rely on friends and family members, the media, and the Internet, rather than health-care professionals as top sources of CAM information.[13,14] Information obtained from these nonprofessional sources is often inaccurate. A majority of patients used botanicals or other supplements, expecting them to suppress the growth of cancer or even cure cancer,[13,14] not realizing that most such effects come from *in vitro* or animal studies. There has been little evidence to date showing any CAM therapies can achieve those effects in clinical settings. Many supplements are often produced with minimal if any quality control.[15] They may interact with many prescription medications, including chemotherapy, possibly decreasing efficacy or increasing toxicity.[16,17] Some patients use dietary supplements nondiscriminatorily for possible benefits in cancer prevention and cancer treatment. However, some supplements may do more harm than good (*eg*, supplementation of beta-carotene may actually increase the risk of

lung cancer in those who currently smoke and in those who recently quit smoking).[18,19] However, therapies backed by supportive evidence for symptom control and favorable risk/benefit ratios, such as acupuncture and mind-body techniques, were used less frequently than were botanicals.[13,14]

Two further barriers that hinder open communication on CAM use are the perceived lack of familiarity with CAM modalities and the widespread dismissive attitude among mainstream health-care professionals. Medical degree courses rarely include review of common CAM therapies, and many physicians who provide care to cancer patients are unable to discuss these approaches in an open, patient-centered fashion. Increasing numbers of educational resources, including review articles, books, continuing medical education courses, and reliable Web sites, are available to interested physicians, nurses, and other practitioners.

Major cancer centers in North America and elsewhere have established integrative medicine programs to study and combine helpful complementary therapies with mainstream oncology care, while educating cancer patients to avoid potentially harmful "alternative" therapies and herb-drug interactions. They are valuable and yet underutilized resources for busy oncologists who may not have the time for an in-depth discussion with patients on CAM. An international organization has been established to encourage appropriate clinical integration and scientific evaluation and dissemination of evidence-based information (Society for Integrative Oncology, http://www.integrativeonc.org).

Mind-Body Techniques

RECOMMENDATION

3. In lung cancer patients, mind-body modalities are recommended as part of a multidisciplinary approach to reduce anxiety, mood disturbance, or chronic pain. Grade of recommendation, 1B

Rationale and Evidence: Mind-body modalities, including meditation, hypnosis, relaxation techniques, cognitive-behavioral therapy, biofeedback, and guided imagery are increasingly becoming part of mainstream care over the years. A survey found that 19% of American adults used at least one mind-body therapy in a 1-year period.[20] The 2002 US nationwide survey[5] showed 12% of the respondents used deep breathing relaxation techniques and 8% used meditation. A metaanalysis[21] of 116 studies found that mind-body therapies could reduce anxiety, depression, and mood disturbance in cancer patients, and assist their coping skills. Mind-body techniques also may help reduce chronic low back pain, joint pain, headache, and procedural pain.[22]

Meditation: Meditation focuses attention on increasing mental awareness and clarity of mind (concentrative meditation) or opens attention to whatever goes through the mind and to the flow of sensations experienced from moment to moment (mindfulness meditation). In a randomized wait-list control study[23] of 109 cancer patients, participation in a 7-week mindfulness-based stress reduction program was associated with significant improvement in mood disturbance and symptoms of stress. A single-arm study[24] of patients with breast and prostate cancer showed significant improvement in overall quality of life, stress, and sleep quality, but symptom improvement was not significantly correlated with program attendance or minutes of home practice.

Yoga: Yoga, which combines physical movement, breath control, and meditation, improved sleep quality in a trial of 39 patients with lymphoma. Practicing a form of yoga that incorporates controlled breathing and visualization significantly decreased sleep disturbance when compared to wait-list control subjects.[25] Mindfulness-based stress reduction techniques must be practiced to produce beneficial effects.[26]

Hypnosis: Hypnosis is an artificially induced state of consciousness in which a person is highly receptive to suggestions. A trancelike state (similar to deep daydreaming) can be achieved by first inducing relaxation and then directing attention to specific thoughts or objects. For best results, the patient and the therapist must have a good rapport with a level of trust; the environment must be comfortable and free from distractions; and the patient must be willing to undergo the process and must desire to be hypnotized. Research shows that hypnosis is beneficial in reducing pain, anxiety, phobias, and nausea and vomiting.

In one study, 20 patients who underwent excisional breast biopsy were randomly assigned to a hypnosis or control group (standard care). Postsurgery pain and distress were reduced in the hypnosis group.[27] In another study, children undergoing multiple painful procedures such as bone marrow aspiration or lumbar puncture were randomized to receive hypnosis, a package of cognitive behavioral coping skills, or no intervention. Those who received either hypnosis or cognitive behavioral therapy experienced more pain relief than did control patients. The effects were similar between hypnosis and cognitive behavioral therapy. Both therapies also reduced anxiety and distress, with hypnosis showing

greater effectiveness.[28] Hypnosis was studied in a randomized controlled trial[29] of 60 patients undergoing elective plastic surgery. Perioperative and postoperative anxiety and pain were significantly reduced in the hypnosis group when compared to the control group who just received stress reduction training. Reduction in anxiety and pain was achieved along with significant reduction in intraoperative requirements for sedatives and analgesics.[29]

In a study[30] of 67 patients who underwent bone marrow transplantation, subjects were randomized to one of the four intervention groups: hypnosis training, cognitive behavioral coping skills training, therapist contact control, or usual care. Oral pain from mucositis was reduced in the hypnosis group. An NIH Technology Assessment Panel found strong evidence for hypnosis in alleviating cancer-related pain.[31] Hypnosis effectively treats anticipatory nausea in pediatric[32] and adult cancer patients[33] and reduces postoperative nausea and vomiting.[29]

Selection of proper patients and qualifications of the hypnotherapist contribute to safe hypnotherapy. A small percentage of patients may experience dizziness, nausea, or headache. These symptoms usually result from patients being brought out of trances by inexperienced hypnotherapists.

Relaxation Techniques: Relaxation techniques were shown in randomized controlled trials to ameliorate anxiety and distress significantly. A randomized study of relaxation therapy vs alprazolam showed that both approaches significantly decreased anxiety and depression, although the effect of alprazolam was slightly quicker for anxiety and stronger for depressive symptoms.[34] Relaxation achieves the effect without side effects and at a lower cost. A randomized trial[35] of 82 radiation therapy patients found significant reductions in tension, depression, anger, and fatigue for those who received relaxation training or imagery.

A metaanalysis[36] of 59 studies showed improved sleep induction and maintenance with psychological interventions. Although pharmaceuticals may produce a rapid response, some studies suggest that behavioral therapies help to maintain longer-term improvement in sleep quality. The NIH consensus panel[31] concluded that behavioral techniques, particularly relaxation and biofeedback, produce improvements in some aspects of sleep, but the magnitude of improvement in sleep onset and time may not achieve clinical significance.

Manipulative and Body-Based Practices

Recommendations

4. In lung cancer patients experiencing anxiety or pain, massage therapy delivered by a massage therapist trained in oncology is recommended as part of a multimodality treatment approach. Grade of recommendation, 1C

5. The application of deep or intense pressure is not recommended near cancer lesions or anatomic distortions such as postoperative changes, as well as in patients with a bleeding tendency. Grade of recommendation, 2C

Rationale and Evidence: The many types of body-based practices have in common the manipulation or movement of parts of the body to achieve health benefits. Massage therapists apply pressure to muscle and connective tissue to reduce tension and pain, improve circulation, and encourage relaxation. Massage therapy has variations in techniques, such as Swedish massage, Thai massage, and Shiatsu. Other body-work techniques, such as Alexander Technique and Pilates, address posture and movement, whereas yoga, Tai Chi, Reiki, and polarity therapy incorporate strong mind-body components.[37]

Massage therapy helps relieve symptoms commonly experienced by cancer patients. It reduces anxiety and pain[38–41] as well as fatigue and distress.[38] Anxiety and pain were evaluated in a crossover study[39] of 23 inpatients with breast or lung cancer receiving reflexology (foot massage) or usual care. Patients experienced significant decreases in anxiety; in one of three pain measures, breast cancer patients experienced significant decreases in pain as well.[39] In the largest study[40] to date, 87 hospitalized cancer patients were randomized to receive foot massage or control. Pain and anxiety scores decreased with massage, with differences between groups achieving statistical and clinical significance. The use of aromatic oil seemed to enhance the effect of massage in early studies,[41,42] but significant enhancement was not seen in more recent randomized controlled trials.[43–45] For noncancer subacute and chronic back pain, massage therapy was found effective in a systematic review of randomized controlled trials, and preliminary data suggest it may help reduce the costs of care.[46]

Massage therapy is generally safe when practiced by credentialed practitioners. Serious adverse events are rare and associated with exotic types of massage or untrained practitioners.[47] In work with cancer patients, the application of deep or intense pressure should be avoided, especially near lesions or anatomic distortions such as postoperative changes. Patients with bleeding tendencies should receive only gentle, light-touch massage.

Energy Therapies

RECOMMENDATION

6. For lung cancer patients, therapies based on manipulation of putative bioenergy fields are not recommended. Grade of recommendation, 1C

Rationale and Evidence: Energy therapies are based on the theory that manipulation of "energy fields" around a patient has therapeutic value. Two types of energy fields are involved: biofield and electromagnetic field.

Biofield therapies are intended to affect energy fields that purportedly surround and penetrate the human body. Because no convincing scientific evidence has emerged despite decades of attempt to prove the existence of such fields, some of the therapies, although originally developed from the theory of bioenergy fields, likely exert their effects on patients through light touch or mind-body interaction. Such therapies include Qi-gong, Reiki, and therapeutic touch. This type of therapy is reviewed in the "Mind-Body Techniques" section.

Bioelectromagnetic-based therapies involve the unconventional use of electromagnetic fields, such as pulsed fields, magnetic fields, or alternating-current fields or direct-current fields. Most research in bioelectromagnetics focuses on genotoxicity of environmental electromagnetic fields, such as whether exposure to power lines or cell phones increases the risk of cancer.[48–50] There has been no report showing the bioelectromagnetic therapies to be effective in cancer treatment or symptom control.

Acupuncture

Acupuncture is a modality that originated from traditional Chinese medicine. The theory was that one can regulate the flow of "Qi" (vital energy) by the stimulation of certain points on the body with needles, heat, or pressure. Scientific research[51,52] suggests that the effects of acupuncture are likely mediated by the nervous system. Release of neurotransmitters and change of brain-functional MRI signals are observed during acupuncture. Acupuncture was used traditionally for almost every ailment; few such applications are supported by rigorous clinical studies. However, evidence supports the use of acupuncture in treating some common symptoms experienced by cancer patients and others.

RECOMMENDATION

7. Acupuncture is recommended as a complementary therapy when pain is poorly controlled or when side effects such as neuropathy or xerostomia from other modalities are clinically significant. Grade of recommendation, 1A

Rationale and Evidence: Pain is the most common and the best-studied indication for acupuncture. Acupuncture relieves both acute (*eg*, postoperative dental pain) and chronic (*eg*, headache) pain.[53,54] An NIH consensus statement[53] in 1997 supported acupuncture for adult postoperative pain, chemotherapy-related nausea and vomiting, and postoperative dental pain. Insufficient evidence was available to support other claims of efficacy at that time; but in the ensuing years, many publications have documented the utility of acupuncture as an adjunct treatment for pain, emesis, and other symptoms.

A randomized controlled trial[55] of 570 patients with osteoarthritis of the knee found that a 26-week course of acupuncture significantly improved pain and dysfunction when compared to sham acupuncture control. In this study, all patients received other usual care for osteoarthritis. At 8 weeks, both pain and function improved, but the difference between groups was significant only for function.[55] A companion article[56] reported the results of a randomized controlled trial of acupuncture for chronic mechanical neck pain. Acupuncture was found to reduce neck pain and produce a statistically, but not clinically, significant effect compared with placebo. Data on acute low back pain are inconclusive.[57]

Acupuncture appears effective against cancer-related pain. A randomized placebo-controlled trial[58] tested auricular acupuncture for patients with pain despite stable medication. A total of 90 patients were randomized to have needles placed at correct acupuncture points (treatment group) vs acupuncture or pressure at nonacupuncture points. Pain intensity decreased by 36% at 2 months from baseline in the treatment group, a statistically significant difference compared with the two control groups, for whom little pain reduction was seen.[58] Skin penetration *per se* showed no significant analgesic effect. The authors selected acupuncture points by measuring electrodermal signals. These results are especially important because most of the patients had neuropathic pain, which is often refractory to conventional treatment.

Brain imaging technology is now being used to examine the specific nervous pathways involved in acupuncture. In functional MRI studies, true acupuncture induces brain activation in the hypothalamus and nucleus accumbens, and deactivates areas of the anterior cingulate cortex, amygdala, and hippocampus. Such changes are not observed in control stimulations, which affect only sensory

cortex change. Deactivation of the amygdala and hippocampus has been observed also with electroacupuncture. These data suggest that acupuncture modulates the affective-cognitive aspect of pain perception.[52] Correlations between signal intensities and analgesic effects also have been reported.[59]

Recommendations

8. Acupuncture is recommended as a complementary therapy when nausea and vomiting associated with chemotherapy are poorly controlled. Grade of recommendation, 1B

9. Electrostimulation wristbands are not recommended for managing chemotherapy-induced nausea and vomiting. Grade of recommendation, 1B

Rationale and Evidence: Acupuncture helps lessen chemotherapy-induced nausea and vomiting.[60] In one study,[61] 104 breast cancer patients receiving highly emetogenic chemotherapy were randomized to receive electroacupuncture at the PC6 and ST36 acupuncture points, minimal needling at nonacupuncture points, or pharmacotherapy alone. Electroacupuncture significantly reduced the number of episodes of total emesis from a median of 15 to 5 when compared with pharmacotherapy only. Most patients did not know the group to which they had been assigned.[61] The effects of acupuncture do not appear entirely because of attention, clinician-patient interaction, or placebo.

The combination of acupuncture and serotonin receptor antagonists, the newest generation of antiemetics, showed mixed results. In a trial[62] of patients with rheumatic disease, the combination decreased the severity of nausea and the number of vomiting episodes more than ondansetron alone in patients receiving methotrexate (an agent also used in chemotherapy). However, a study[63] of cancer patients receiving high-dose chemotherapy and autologous stem-cell transplantation reported no significant benefit for ondansetron plus acupuncture vs ondansetron plus placebo acupuncture. Acupuncture also suppresses nausea and vomiting caused by pregnancy,[64] surgery,[65] and motion sickness.[66,67]

Acupressure wristbands that render continuous stimulation of the PC6 point also have been tested for chemotherapy-related nausea and vomiting. In a randomized controlled trial[68] of 739 patients, nausea on the day of chemotherapy was reduced significantly in patients wearing wristbands compared with no-band control subjects. No significant differences were found for delayed nausea or vomiting. Unlike acupressure wristbands, expected efficacy of electrostimulation wristbands was not significantly related to any component of nausea or to antiemetic use. It was believed that the electrical stimulus generated by the electrostimulation band could act as a conditioned stimulus (akin to a reminder) of the nausea that patients are trying to control, and thereby actually accentuate the development of nausea in some individuals.[68]

Recommendation

10. When the patient with lung cancer does not stop smoking despite use of other options, a trial of acupuncture is recommended to assist in smoking cessation. Grade of recommendation, 2C

Rationale and Evidence: Smoking cessation has the largest impact in preventing lung cancer. Educational, behavioral, and medical interventions are the mainstay for smoking cessation. The effect of acupuncture has been studied with mixed results. A metaanalysis[69] of 22 studies concluded that acupuncture is no more effective than placebo in smoking cessation; however, the same metaanalysis found that acupuncture did no worse than any other intervention. A more recent randomized trial[70] of 141 subjects tested auricular acupuncture, education, or the combination in achieving smoking cessation. The authors found that both modalities, alone or in combination, significantly reduced smoking. The combination showed a significantly greater effect in subjects with a greater pack-year history.[70]

Brain imaging studies show that smoking suppresses blood flow to anterior cingulate cortex, hippocampus, and amygdala.[71] Curiously, these are the same areas suppressed by acupuncture.[52] Given the huge public health impact of smoking and the imperfect results of existing smoking cessation techniques, it is acceptable, although not encouraged, for someone who has been unable to quit smoking to try acupuncture. Further studies using refined acupuncture techniques guided by recent advances in acupuncture research appear warranted.

Recommendation

11. In patients with lung cancer with symptoms such as dyspnea, fatigue, chemotherapy-induced neuropathy, or postthoracotomy pain, a trial of acupuncture is recommended. Grade of recommendation, 2C

Rationale and Evidence: Lung cancer patients with advanced disease almost always experience

dyspnea attributable to parenchymal tumor burden or pleural effusion. Oxygen and opioids remain the mainstay of symptomatic treatment, although confusion and constipation are common side effects. An uncontrolled study[72] in cancer patients receiving palliative care showed marked reduction of dyspnea scores after a session of acupuncture. However, subsequent randomized, sham, controlled trials[73] did not show significant improvement in subjective sensation of dyspnea in patients with advanced lung or breast cancer.

Fatigue after chemotherapy or irradiation, another major and common problem, has few reliable treatments in patients without a correctable cause such as anemia.[74] In an uncontrolled trial[75] of fatigue after chemotherapy, acupuncture reduced fatigue 31% after 6 weeks of treatment. Among those with severe fatigue at baseline, 79% had nonsevere fatigue scores at follow-up,[75] whereas fatigue was reduced only in 24% of patients receiving usual care in another center.[76]

Although acupuncture is commonly used to treat neuropathy, most previous research was performed in HIV-related neuropathy or diabetic neuropathy. Patients with HIV-related peripheral neuropathy were treated with standardized acupuncture regimen or control point regimen in a randomized controlled trial[77] of 239 patients. Reduction of pain scores was observed in both groups, and no significant difference between the groups was seen. Forty-six diabetic patients with chronic painful peripheral neuropathy were treated with acupuncture in a single-arm study. Significant improvement of symptoms was reported by 77% of patients, a percentage higher than the usual response to placebo observed in pain trials. There was no significant change in the peripheral neurologic examination scores.[78] No clinical trial of acupuncture for chemotherapy-induced neuropathy has been reported, although a recent small case series[4] showed positive results. A randomized clinical trial to evaluate acupuncture in the treatment of postthoracotomy neuropathic pain is underway.

If these symptoms become a significant clinical problem in a particular patient despite conventional treatment, it is not unreasonable to accept a patient's choice to try acupuncture for symptom reduction. The lack of conclusive evidence supporting its effectiveness is balanced to the favorable safety record of acupuncture and the lack of other viable treatment options.

Recommendation

12. In patients with a bleeding tendency, it is recommended that acupuncture be performed by qualified practitioners and used cautiously. Grade of recommendation, 1C

Rationale and Evidence: Acupuncture needles are regulated as medical device in the United States. They are filiform, sterile, single use, and very thin (28 to 40 gauge). Insertion of acupuncture needles causes minimal or no pain and less tissue injury than phlebotomy or parenteral injection. Acupuncture performed by experienced, well-trained practitioners is safe. Only six cases of potentially serious adverse events were reported in a recent study of 97,733 patients receiving acupuncture in Germany. They included exacerbation of depression, hypertensive crisis, vasovagal reaction, asthma attack, and pneumothorax. The most common minor adverse events included local bleeding and needling pain, both in $< 0.05\%$ of patients.[79] It is prudent to avoid acupuncture at the site of tumor or metastasis, limbs with lymphedema, areas with considerable anatomic distortion attributable to surgery, and in patients with thrombocytopenia, coagulopathy, or neutropenia. Cancer patients require certified practitioners who are experienced in treating patients with malignant diseases.

Diet and Dietary Supplements Including Herbal Products

Many epidemiology studies demonstrate an association of diet and cancer incidence. Other than smoking cessation, a healthy diet is perhaps the most important lifestyle change a person can make to help prevent cancer, as well as cardiovascular disease and diabetes. However, aside from interventions to counter specific protein, calorie, vitamin, or mineral nutritional deficits, special dietary regimens do not have any significant role in cancer treatment. Some dietary regimens have been promoted for cancer treatment, such as macrobiotic diet or alkaline diet. None has been supported by clinical studies.

The use of biological-based CAM such as herbs and other dietary supplements is very popular among cancer patients.[13,14,80] Most users expect the supplements to help cancer treatment or reduce side effects. Such expectations are often unmet.[14] The purported benefits of the supplements are usually only supported by preclinical studies. Only a few were evaluated in clinical trials. The concurrent use of supplements, especially high-dose antioxidants or complex botanical agents, during chemotherapy or radiation therapy can be problematic because of drug-supplement interaction.[81,82] Some botanicals, based on their chemical structure, may have adverse effects in perioperative use. Their antiplatelet ac-

tivity may adversely interact with corticosteroids and CNS depressant drugs; they may produce GI effects, hepatotoxicity, and nephrotoxicity; and can produce additive effects when used concomitantly with opioid analgesics.[83] Quality control and adulteration of dietary supplements are additional major issues.[84]

Recommendations

13. It is recommended that dietary supplements, in particular herbal products, be evaluated for side effects and potential interaction with other drugs. Those that are likely to interact with other drugs, such as chemotherapeutic agents, should not be used concurrently during chemotherapy or radiation, or before surgery. Grade of recommendation, 1B

14. In lung cancer patients who either do not respond to or decline antitumor therapies, it is recommended use of botanical agents occur only in the context of clinical trials. Grade of recommendation, 1C

Rationale and Evidence: Dietary supplements include vitamins, minerals, herbs or other botanicals, amino acids, and other substances intended to supplement the diet. They are usually natural products with a record of historical use. By law, the manufacturers are not allowed to claim that their product will diagnose, cure, mitigate, treat, or prevent a disease. However, patients often take them with such expectations.

Botanicals and other natural products are a valuable source for the development of therapeutic agents, where they are carefully studied for safety and efficacy. Approximately one fourth of prescription drugs contain active ingredients derived from plants, including several chemotherapeutic agents (paclitaxel, docetaxel), camptothecins (irinotecan, topotecan), and vinca alkaloids (vincristine, vinorelbine). Sold as dietary supplements, however, they are rarely produced to the same high standards. Some herbs cause significant side effects. Detrimental herb-drug interactions may occur. Finally, product inconsistency and contamination have been reported.[84,85]

Most claims made by producers of herbal supplements are based on historical experience, unconfirmed by clinical trials. Many herbs show direct antitumor activity in *in vitro* or animal experiments,[86,87] but translating preclinical to clinical use often fails because the active constituents, often unknown, are insufficiently potent or metabolized before reaching their target. The composition of herbs is complex and typically containing hundreds of constituents. Moreover, some herbal remedies function through the synergistic effects of their multiple constituents, hindering identification of active components.

Herbs and other botanical products that enhance immune function are especially popular among cancer patients and may prove useful in cancer treatment or prevention. Some show immunomodulatory effects in preclinical studies, assisting tumor rejection or resistance to pathogens.[88–90] However, the most popular immune boosting herb in the United States used commonly to treat colds, echinacea, showed disappointing results in randomized controlled trials.[91–93]

Because botanicals contain biologically active constituents, they carry health risks if not used properly. The botanical kava kava, for example, proved more effective than placebo in treating anxiety, stress, and insomnia,[94,95] and it was considered a viable alternative to benzodiazepines because of its benefits and absence of dependency and addiction. However, later reports associate this herbal remedy with severe hepatotoxicity resulting in death.[96]

Herbal medicine was practiced historically by those with at least some knowledge of side effects of the herbs. Today, however, many herbal and other botanical products are readily available to US consumers under the Dietary Supplement Health and Education Act of 1994, which regulates them only as food supplements and requires no previous studies of safety and efficacy. A few herbal products have been removed from the market by the Food and Drug Administration because of adverse events. A recent example is agents that contain ephedra because its sympathomimetic activity has been associated with cardiovascular complications, including death.

Herbs may attenuate or lessen the effect of a drug either by direct action on its target or by altering its pharmacokinetics.[17,97] Herbs such as feverfew, garlic, ginger, and ginkgo have anticoagulant effects and should be avoided by patients using warfarin, heparin, aspirin, and related agents. Red clover, Dong quai, and licorice, because of their phytoestrogen components, should not be used by patients using tamoxifen or aromatase inhibitors. St. John wort was a popular product for depression, at least equivalent in efficacy to tricyclics and selective serotonin reuptake inhibitors in mild to moderate depression and with a side effect profile superior to both.[98,99] It was found, however, that St. John wort induces cytochrome P450 CYP3A4. Reduced plasma levels of SN38, an active metabolite of irinotecan, have been reported after simultaneous use.[100] Such metabolic interactions preclude St. John wort for patients on medications metabolized by CYP3A4.[101]

Although not an herb, grapefruit juice was found

to significantly change the plasma level of many prescription drugs. Further study found that furanocoumarin derivatives inhibit intestinal CYP3A4, which consequently increases the bioavailability of drugs that are substrate to first-pass metabolism by this enzyme.[102,103] Interestingly, such interaction initially was discovered by accident in an ethanol-calcium channel blocker interaction study in which grapefruit juice was used as the vehicle for the alcohol.[104] Details of herbs-drug interactions can be found at several sources.[85,105]

Recommendation

15. It is recommended that patients be advised to avoid therapies promoted as "alternatives" to mainstream care. Grade of recommendation, 1A

Rationale and Evidence: Alternative therapies that claim to improve survival have largely been demonstrated to be ineffective in clinical trials.[106] Randomized trials have shown no benefit or, in some cases, shorter survival for high-dose vitamin C,[107,108] shark cartilage,[109] hydrazine sulfate,[110–113] and mistletoe extracts.[114–117] Cohort or phase II studies have shown no benefit to DiBella therapy,[118,119] antineoplastons,[120] Livingston-Wheeler therapy,[121] amygdalin,[122] and Pau D'arco.[123] In a population-based study,[124] patients using alternative therapy have been shown to have shorter survival, after adjustment for known prognostic factors, than those avoiding such therapies.

Research Priorities

We view the following as high-priority areas of research: effectiveness of complementary therapies in the management of symptoms or disease processes for which our current treatment options are not satisfactory; mechanisms of action as explained by contemporary biomedical science; definitive database of drug-supplement interactions; and new cancer therapies derived from botanicals or other supplements or their synergistic effect with conventional medicine.

Conclusion

The use of CAM is common among cancer patients. These therapies are very diverse in their origin, theory, practice, safety, and efficacy. Some of the therapies have been shown in studies to be helpful in reducing symptoms experienced by cancer patients. These complementary therapies (used as adjuncts to mainstream cancer treatment) are increasingly integrated into regular oncologic care, leading to integrative oncology. Dietary supplements, herbs, and other botanicals can be problematic because of their adverse effects or interactions with chemotherapy, radiotherapy, or surgery. There are those therapies promoted as "alternative" to mainstream cancer treatment. Patients who use these "alternative" therapies are at risk for missing the window of opportunity for effective treatment. It is important for all involved in the care of cancer patients to help patients distinguish between the two, and to approach complementary and alternative therapies appropriately to receive benefit while avoiding harm. Specific advice should be provided after considering the level of evidence and the risk-to-benefit ratio. Health-care professionals should know where to find reliable sources of information.

Summary of Recommendations

1. It is recommended that all patients with lung cancer be specifically asked about the use of CAM. Grade of recommendation, 1C

2. It is recommended that all patients with lung cancer be given guidance about the advantages and disadvantages of complementary therapies in an open, evidence-based, and patient-centered manner by a qualified professional. Grade of recommendation, 1C

3. In lung cancer patients, mind-body modalities are recommended as part of a multimodality approach to reduce anxiety, mood disturbances, or chronic pain. Grade of recommendation, 1B

4. In lung cancer patients experiencing anxiety or pain, massage therapy delivered by an oncology-trained massage therapist is recommended as part of a multimodality treatment approach. Grade of recommendation, 1C

5. The application of deep or intense pressure is not recommended near cancer lesions or anatomic distortions, such as postoperative changes, as well as in patients with a bleeding tendency. Grade of recommendation, 2C

6. For lung cancer patients, therapies based on putative manipulation of bioenergy fields are not recommended. Grade of recommendation, 1C

7. Acupuncture is recommended as a complementary therapy when pain is poorly controlled or when side effects, such as neuropathy or xerostomia from other modalities, are clinically significant. Grade of recommendation, 1A

8. Acupuncture is recommended as a complementary therapy when nausea and vomiting associated with chemotherapy are poorly controlled. Grade of recommendation, 1B

9. Electrostimulation wristbands are not recommended for managing chemotherapy-induced nausea and vomiting. Grade of recommendation, 1B

10. When the patient with lung cancer does not stop smoking despite use of other options, a trial of acupuncture is recommended to assist in smoking cessation. Grade of recommendation, 2C

11. In patients with lung cancer with symptoms such as dyspnea, fatigue, chemotherapy-induced neuropathy, or postthoracotomy pain, a trial of acupuncture is recommended. Grade of recommendation, 2C

12. In patients with a bleeding tendency, it is recommended that acupuncture be performed by qualified practitioners and used cautiously. Grade of recommendation, 1C

13. It is recommended that dietary supplements, particularly herbal products, be evaluated for side effects and potential interactions with other drugs. Those that are likely to interact with other drugs, such as chemotherapeutic agents, should not be used concurrently during chemotherapy or radiation, or before surgery. Grade of recommendation, 1B

14. In patients with lung cancer who either do not respond to or decline antitumor therapies, it is recommended that use of botanical agents occur only in the context of clinical trials. Grade of recommendation, 1C

15. It is recommended that patients be advised to avoid therapies promoted as "alternatives" to mainstream care. Grade of recommendation, 1A

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